REMARKS

Claims 1, 4-6, 11, 13-23, 25-33 and 37-53 are pending in this application. Claims 43-52 have been withdrawn from consideration deemed non-elected subject matter. Claims 1, 4-6, 11, 13-23, 25-33 and 37-42 were variously rejected under 35 U.S.C. § 112, first paragraph. Claims 1, 4-6, 11, 13-23, 25-33, 37-42 and 53 were variously rejected under 35 U.S.C. § 112, second paragraph. Claims 1, 4, 6, 11, 13-14, 17, 20-23, 25-33, 37 and 40-42 were variously rejected under 35 U.S.C. § 103.

By this amendment, claims 4-6 have been canceled and claims 1, 37, 40 and 53 have been amended without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments can be found, *inter alia*, throughout the specification, for example, at page 10, lines 16-18.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1, 4-6, 11, 13-23, 25-33, 37-42 and 53 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

Although Applicants believe that the claims were sufficiently definite when considered in view of the specification and the understanding of those of skill in the art, Applicants have attempted to respond to the concerns of the Examiner in order to facilitate disposition of the present case.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1, 4-6, 11, 13-23, 25-33 and 53 were rejected under 35 U.S.C. §112, first paragraph, for allegedly not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. Applicants respectfully traverse this rejection.

The Examiner states that the specification is enabling for methods for modulating a Th1 immune response by co-administering the second antigen with an ISS-antigen complex, but not for "modulating a Th-1 response against a second antigen that is administered after the administration of an ISS-antigen complex or modulating a Th-1 response to a second antigen that is co-administered with the ISS-antigen complex at a different site of administration from the ISS-antigen complex." Office Action, page 3.

Applicants respectfully point out that the claims are directed to "co-administering" the complex and the second antigen to the individual. The specification defines "co-administration" as "the administration of at least two different substances sufficiently close in time to modulate an immune response" and provides simultaneous administration as an example of co-administration. See, for example, specification page 13, lines 12-15. Thus, by definition, the claimed invention is not directed to administering the complex and the second antigen at vastly different times.

As noted by the Examiner, the experiments presented on pages 52-54 of the specification demonstrate that the protocol of administering the second antigen 4 and 8 weeks after administration of the complex was not successful in stimulating a Th1 response to the second antigen. However, such a protocol is not currently claimed. Thus, Applicants respectfully submit that the specification enables the claims to co-administration as commonly understood and defined in the specification.

With regard to the Examiner's assertion that administration of the complex at a "different site" than the administration of the second antigen is not enabled, Applicants respectfully disagree with this assertion and interpretation of the experimental results.

The data presented in Table 6 indicate that co-administration of the complex and the second antigen (βgal) on the same day but at different sites (ID vs IM), results in a greater anti-βgal IgG2a response than that from the administration of βgal alone. In fact, co-administration of 10 μg of the complex intradermally in the tail and of βgal intramuscularly in the thigh resulted in a statistically significant 4-fold increase in the anti-βgal IgG2a response over that from the administration of βgal alone. Although the increase in the Th1 response following co-administration at two different sites (4-fold) is less that the increase in the Th1 response following co-administration at the same site (54-fold), the experimental results demonstrate that co-administration of the complex and β-gal at two different sites results in an increased Th1 response.

Thus, Applicants respectfully submit that the specification teaches how to make and use the claimed invention without undue experimentation. Applicants respectfully submit that the specification enables co-administration of the complex and the second antigen at different sites in the individual.

Applicants respectfully submit that a *prima facie* case for lack of enablement has not been established and that the pending claims are in compliance with the enablement requirements.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. §103

Claims 1, 4, 6, 11, 13-14, 17, 20-23, 25-33, 37 and 40-42 were rejected under 35 U.S.C. §103 as allegedly unpatentable over Schwartz et al. (WO 98/55495, "Schwartz"). Claims 1, 4, 6, 11, 13-14, 17, 20-23, 25-33, 37 and 40-42 were rejected under 35 U.S.C. §103 as allegedly unpatentable over Carson et al. (WO 98/16247, "Carson"). Claim 5 was rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson further in view of Rose (*J. Ther. Biol.* 195:111-128 (1998)). Claims 15 and 38 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson and further in view of Lee et al. (*Ann. Med.* 30:460-468 (1998), "Lee"). Claims 16 and 39 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson and further in view of Durali et al. (*J. of Virol.* 72(5):3547-3553 (1998), "Durali"). Claims 18 and 19 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson and further in view of Anderson (US Patent No. 4,673,574).

Applicants respectfully traverse these rejections.

A *prima facie* case of obviousness requires that three basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Finally, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20USPQ2d 1438 (Fed. Cir. 1991); MPEP §2143. If any one of these three criteria is not met, a *prima facie* case of obviousness has not been established. As presented below, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

The amended claims are directed to a method of modulating an immune response to a second antigen through co-administration of (i) a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen and (ii) a second antigen, where the amount of the complex administered is sufficient to modulate an immune response to the second antigen. The claimed invention is also directed to a composition comprising (i) a complex comprising an immunomodulatory polynucleotide covalently conjugated to a viral conserved polypeptide (first antigen) and (ii) a viral variable polypeptide (second antigen) and to a composition comprising (i) a complex comprising an immunomodulatory polynucleotide covalently conjugated to an allergen (first antigen) and (ii) a second antigen.

Claims 1, 4, 6, 11, 13-14, 17, 20-23, 25-33, 37 and 40-42 over Schwartz or Carson.

Both Schwartz and Carson describe immunomodulatory activity of an ISS-antigen conjugate composition and of an ISS + antigen admixture. The Examiner acknowledges that Schwartz and Carson do "not explicitly teach administering a second antigen with the [ISS-antigen] composition." Office Action, pages 9 and 12. However, the Examiner asserts that "administering a second antigen with a complex comprising an ISS-antigen complex would have been obvious from the teachings" of Schwartz and Carson. Office Action, pages 10 and 12. Applicants respectfully disagree with this assertion.

As outlined in the record in responses to previous Office Actions, neither Schwartz or Carson teach or suggest the claimed invention, *i.e.*, co-administering an ISS-first antigen conjugate and a second antigen to modulate an immune response to the second antigen. There is no teaching or suggestion of the claimed invention in the cited references.

The Examiner states that "Schwartz suggests that the immunomodulatory compositions comprise at least one antigen, see page 5, lines 1-2 and page 12, lines 9-15." Office Action, page 9. However, the Schwartz citation at page 5 states that the "composition comprises an oligonucleotide with at least one ISS, an antigen and an adjuvant" (emphasis added) and not "at least one antigen" as

stated in the Office Action. Also, the Schwartz citation at page 12 discloses an ISS plus one or more members of the group of antigen, facilitator and adjuvant. Thus, Schwartz suggests the combinations of ISS and antigen of: ISS + antigen, ISS + antigen + facilitator, ISS + antigen + adjuvant, ISS + antigen + facilitator + adjuvant. Schwartz never suggests ISS + antigen 1 + antigen 2. Indeed, the remainder of Schwartz supports this interpretation in that there are no examples or claims of ISS + multiple antigens.

With regard to Carson, the Examiner has not provided any citations in Carson to support Carson teaching or suggesting co-administration of an ISS-antigen complex and a second antigen.

Further, there is no suggestion or motivation in the references or in the art to modify Schwartz or Carson to arrive at the claimed invention. Applicants maintain that neither Schwartz nor Carson provide a reasonable expectation of success of the claimed invention.

The Examiner states that "Schwartz teaches that ISS oligonucleotides are art-recognized as being Th1 stimulatory molecules when administered with an antigen, see page 3, lines 32-35 and claims 47 and 48." Office Action, page 10. Applicants note that, at page 3, lines 28-40, the specification makes it clear that ISS oligonucleotides are specific Th1 stimulatory molecules in that they stimulate the production of IgG specifically against the co-administered antigen. Schwartz, however, does not teach or suggest that the administration of the ISS-antigen complex and a second antigen would result in a specific Th1 response to the second antigen.

Given that both references demonstrate some antigen-specific immunostimulatory activity of an ISS and antigen admixture and of an ISS-antigen complex, the Examiner supports the assertion of obviousness by stating that "one of ordinary skill in the art would expect induction of a Th1 against any of the complexed or non-complexed antigens." Office Action, page 10. The Examiner appears to argue that one would expect the claimed ISS-antigen complex to behave as an uncomplexed ISS molecule relative to the co-administered second antigen. If the ISS-antigen complex were to provide immunostimulatory activity for the second antigen similarly to an

uncomplexed ISS molecule, the expected activity of the complex and the second antigen would be similar to the activity obtained with an ISS + antigen admixture. Applicants respectfully point out that this prediction does not match the observed result.

As presented in Dr. Van Nest's declaration (submitted October 23, 2002), co-administration of the ISS-first antigen complex and the second antigen (βgal) results in an unexpectedly greater Th1 immune response to the second antigen (e.g., IgG2a antibodies and IFN-γ) than that obtained with administration of the ISS + antigen (βgal) admixture. Van Nest Declaration, Exhibits A and B. For example, the amount of anti-βgal (second antigen) IgG2a antibodies produced in response to the co-administration of the ISS-first antigen complex and the second antigen was at least 4 or 9 times the amount of antibody produced in response to the admixture of ISS + antigen. Van Nest Declaration, Exhibit A. Also, the IFN-γ response to βgal (second antigen) upon co-administration of the ISS-first antigen complex and the second antigen was about 3 times to nearly 10 times the IFN-γ response upon administration of an ISS + antigen admixture. Van Nest Declaration, Exhibit B.

Co-administration of a second antigen with the complex resulted in an unexpectedly greater immune response to the second antigen than that observed with administration of the antigen and an uncomplexed ISS in an admixture. Data presented in the specification and in the Van Nest Declaration also indicate a greater suppression of a Th2 response to the second antigen with co-administration of a second antigen with the complex. Thus, Applicants respectfully point out that the claimed methods and compositions of the present invention produced results well beyond expectation.

As outlined on pages 7 and 8 of the specification, this increased immunomodulatory activity of the claimed invention provides a number of benefits and advantages including administration of lower dosages to achieve an effective result.

Finally, the Examiner states that "Carson teaches that ISS molecules induce a Th-1 response to an antigen, see page 11, lines 21-28." Office Action, page 12. However, the Carson citation at page 11, lines 18-21, describes that the ISS-antigen conjugate may be taken up and processed by the cell differently than an antigen not conjugated to a oligonucleotide. Thus, Carson teaches away from using an ISS-antigen conjugate to modulate an immune response to a second, unconjugated antigen.

In sum, Applicants respectfully submit that a *prima facie* case of obvious has not been made.

Even if it was argued that a *prima facie* case is made (which it decidedly is not), Applicants respectfully point out that the claimed method and composition results in an unexpected and very different response than any predicted response that would flow from the teachings of Schwartz or Carson. The unexpected immune response associated with the claimed invention also is of practical significance and benefit as discussed in the specification.

Thus, Applicants respectfully submit that the claimed invention is not obvious in view of either Schwartz or Carson.

Claim 5 over Schwartz or Carson further in view of Rose.

Although Applicants respectfully traverse this rejection for reasons on record, claims 5 has been herein cancelled. Accordingly, this rejection is now moot.

Claim 15 and 38 over Schwartz or Carson and further in view of Lee.

Claims 15 and 38 are directed to a method and a composition of the invention in which the first antigen is influenza nucleocapsid protein. As outlined above, neither Schwartz nor Carson teach or suggest the claimed invention and the claimed invention is not obvious over Schwartz or Carson. Lee describes that ISS within DNA vaccines result in a Th1 immune response to the

encoded antigen and describes the use of DNA vaccines encoding influenza proteins in tests for infection protection.

Lee does not supply what is missing from the primary reference, Schwartz or Carson, and the combinations of Schwartz or Carson and the secondary reference does not teach or suggest the claimed invention, thus do not render the claimed invention obvious.

None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through co-administration of the second antigen and a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen. Also, none of the references, either alone or in combination, describes or suggests the composition as claimed.

Further, Applicants submit that there in no suggestion in the art or in these references to modify their teachings to arrive at the claimed invention.

Claims 16 and 39 over Schwartz or Carson and further in view of Durali.

Claims 16 and 39 are directed to a method and a composition of the invention in which the first antigen is HIV gag protein. As outlined above, neither Schwartz nor Carson teach or suggest the claimed invention and the claimed invention is not obvious over Schwartz or Carson. Durali describes production of cytotoxic T lymphocytes against HIV antigens from various HIV clades.

Durali does not supply what is missing from the primary reference, Schwartz or Carson, and the combinations of Schwartz or Carson and the secondary reference do not teach or suggest the claimed invention, thus do not render the claimed invention obvious.

None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through co-administration of the second antigen and a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen.

Also, none of the references, either alone or in combination, describes or suggests the composition as claimed.

Further, Applicants submit that there in no suggestion in the art or in these references to modify their teachings to arrive at the claimed invention.

Claims 18 and 19 over Schwartz or Carson and further in view of Anderson.

Claim 18 is directed to a method of the invention in which the first antigen is diphtheria toxin mutant (CRM197). Claim 19 is directed to a method of the invention in which the first antigen is diphtheria toxoid. As outlined above, neither Schwartz nor Carson teach or suggest the claimed invention and the claimed invention is not obvious over Schwartz or Carson. Anderson describes diphtheria toxoid and diphtheria CRM 197 as carriers in vaccine preparations.

Anderson does not supply what is missing from the primary reference, Schwartz or Carson, and the combinations of Schwartz or Carson and the secondary reference do not teach or suggest the claimed invention, thus do not render the claimed invention obvious.

None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through co-administration of the second antigen and a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen.

Further, Applicants submit that there in no suggestion in the art or in these references to modify their teachings to arrive at the claimed invention.

In sum, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103.

CONCLUSION

Applicants believe that all issues raised in the Office action have been properly addressed in this amendment and response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882000800.

Respectfully submitted,

Dated: September 2, 2003 By: _____

Karen R. Zachow
Registration No. 46,332

Morrison & Foerster LLP
3811 Valley Centre Drive, Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5191
Facsimile: (858) 720-5125

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